REMARKS

I. Amendments

By this amendment, claims 2-10 have been amended; new claims 13-27 have been added and claims 11 and 12 have been cancelled.

Claim 1 has been amended to incorporate the subject matter of now cancelled claim 11.

A reference to related patent applications has been inserted in the specification.

This amendment adds no new matter to the specification

No amendment of inventorship is necessitated by this amendment.

Support for the new claims 13-27 is found in the specification and claims as originally filed, and for example:

Claim 13, on page 16, lines 17-19;

Claims 14-15, on page 18, lines 9-10;

Claim 16, on page 18, line 11;

Claims 17-21, on page 18, lines 12-13,

Claims 22-26, on page 18, line 14; and

Claim 27 on page 20, line 14.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached pages are captioned "Version with Markings to Show Changes Made".

II. Traverse of the Rejection under 35 U.S.C. Sec. 112, Second Paragraph

Claims 1-12 have been rejected under 35 U.S.C. Sec. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Specifically, the Office Action stated that the expression "TNF-α" is not defined by the claims.

By this amendment, the claims now recite "Tumor Necrosis Factor-alpha".

Therefore, Applicants respectfully request withdrawal of the Sec. 112, second paragraph rejection.

III. Traverse of the Rejection under 35 U.S.C. Sec. 102(b) over Stevenson *et al.*

Claims 1-9 and 11 have been rejected under 35 U.S.C. Sec. 102(b) over Stevenson *et al.* (The Diabetes Manual, 1995 article). Specifically, the Office Action stated that to administer an effective amount of ciglitazone, troglitazone or pioglitazone to prevent a TNF-alpha-mediated inflammatory disease in a mammal would be inherent in the method of treatment disclosed by Stevenson *et al.*

Applicants disagree with the Examiner's interpretation of the asserted art and the asserted rejection based upon inherency. A rejection under 35 U.S.C. §102(b) requires that each and every limitation of the claimed invention be clearly anticipated by the teaching of the asserted art.

The claimed methods are directed to a specific therapeutic treatment of Tumor Necrosis Factor-alpha mediated inflammatory disease in a mammal. The teaching of Stevenson et al. does not anticipate the claimed invention.

In making the present rejection, the Examiner mischaracterizes the teaching of Stevenson *et al.* by improperly ignoring the full context of the teaching. The teaching of Stevenson *et al.* taken as a whole clearly demonstrates the failure of the Examiner's argument. Stevenson *et al.* teach that:

"...a fat-derived cytokine, TNF-α, has been implicated in the production of insulin insensitivity in skeletal muscle."
(Stevenson *et al.* Page 185 first line, last paragraph, *emphasis added*).

Stevenson *et al.* are limited to the context of fat cells and insulin sensitivity in muscle cells and do not contemplate or suggest treatment of a TNF-α mediated inflammatory disease. Stevenson *et al.* further teach that

"Pioglitazone was recently shown to reduce the elevated TNF-alpha mRNA levels by ~50% in fat from k-KA^{y} mice. However, it is not clear if the reduction due to thiazolidinedione treatment is a direct effect of the agents or an indirect consequence of reduction in blood glucose levels and improved insulin action." (Page 186, first paragraph, *emphasis added*).

Thus, the observations of Stevenson *et al.* is limited to the described physiology of fat cells in the context of glucose metabolism and insulin sensitivity. There is no teaching of a therapeutic treatment for TNF-α mediated inflammatory disease. Stevenson *et al.* clearly express uncertainty as to the cause of the described observation. The examiner is ignoring the teaching as a whole in view of Stevenson *et al.* own expressed uncertainty. The Examiner's rejection is made in hindsight, with the benefit of the present application as a guide to interpreting the asserted art. The Examiner has failed to sufficiently support the assertion of an inherent teaching of efficacy of administering thiazolidinedione compound for treating TNF-α mediated inflammatory disease *in vivo*.

The teaching of Stevenson *et al.* is properly limited to the specific description of diabetes, insulin resistance and obesity. No particular therapeutic method is taught by Stevenson *et al.*, only testing of TNF-α with reference to insulin efficacy in the context of glucose disposal. Thus, there is no teaching and no suggestion of all of the limitations of the method of the claimed invention. The claimed invention is not inherently or otherwise disclosed by the teaching of Stevenson *et al.*

The examiner's rejection is defective on its face, since the asserted art fails to teach all the limitations of the claimed invention, either inherently or explicitly.

The Examiner cited case of *Ex parte Novitzki* (26 USPQ2d 1389, BPAI 1993) is inapplicable to the present facts and clearly distinguishable. In Novitzki, the asserted art is a US Patent to Dart which specifically claimed a method for inoculating a plant with a certain bacterial strain to colonize the plant and protect from fungal infection.

> "Dart discloses a method which comprises the step of inoculating a plant with Pseudomonas cepacia type Wisconsin 526, which colonizes the plant. As expressly disclosed by Dart, Pseudomonas cepacia type Wisconsin 526 displays broad-spectrum antifungal activity and, in this regard, we note appellants' recitation of broad-spectrum antifungal activity in claim 5 on appeal. The purpose of Dart's inoculating step is to achieve a method of protecting a plant from fungal disease."
> *Ex parte Novitzki*, 26 USPQ2d 1389 (BPAI 1993)

Another goal

Novitzki's rejected invention recited the same steps for inoculation of plants as claimed by Dart. The expressed method in both the Novitzki application and the Dart patent is to innoculate a plant against infection with a colonizing bacteria.

In the present case, there is no such identity in methods and outcome. The asserted art, and its teaching taken as a whole is only directed towards diabetes and insulin resistance. The claimed invention is directed towards treatment of TNF-α mediated inflammatory disease. One of ordinary skill in the art would not equate the two.

The present facts are clearly distinguishable since the asserted art fails to disclose the claimed method, or any method for a treatment of TNF-α mediated inflammatory disease. The present case is clearly distinguishable from that of *ex parte Novitzki.* The asserted art does not recite any specific method that can anticipate the claimed treatment of TNF-α mediated inflammatory disease.

Since Stevenson *et al.* fail to teach each and every limitation of the claimed invention, the Sec. 102(b) rejection over Stevenson *et al.* must be withdrawn.

IV. Traverse of the Rejection under 35 U.S.C. Sec. 102(b) over Szalkowski *et al.*

Claims 1-9 and 11 have been rejected under 35 U.S.C. Sec. 102(b) over Szalkowski *et al.* (Endocrinology, 1995 article). Specifically, the Office Action stated that to administer an effective amount of ciglitazone, troglitazone or pioglitazone to prevent a TNF-alpha-mediated inflammatory disease in a mammal would be inherent in the method of treatment disclosed by Szalkowski *et al.*

The Examiner mischaracterizes the teaching of Szalkowski *et al.* and fails to consider the teaching as a whole. The specific results described in the cited art are that:

"thiazolidinediones block the inhibitory effect of TNF-α on 3T3-L1 cell differentiation."

"These observations imply that the insulin-sensitizing agents antagonize inhibitory effects of TNFα in adipose tissue."

(Szalkowski *et al.* page 1474, second column, middle to end of last paragraph, *emphasis added*)

The teaching of Szalkowski *et al.* is properly limited to the specific description of diabetes and insulin resistance in the context of adipose tissue. The only method taught by Szalkowski *et al.* is to determine cell division in cultured adipocytes. There is no teaching of any

therapeutic treatment, let alone any treatment for TNF-α mediated inflammatory disease. There is no teaching or suggestion of the claimed invention, nor is the claimed invention inherent in the cell culture limited methods taught by Szalkowski *et al.*

As in the other rejection, once again the asserted *ex parte Novitzki* is inapplicable. The asserted art fails to disclose, describe or hint at the treatment of TNF-α mediated inflammatory disease. The asserted art does not recite any specific method for the treatment of TNF-α mediated inflammatory disease. The present case is clearly distinguishable from that of *ex parte Novitzki.*

Since Szalkowski *et al.* does not teach each and every limitation of the claimed invention the Sec. 102(b) rejection over Szalkowski *et al.* must be withdrawn.

V. Traverse of the Rejection under 35 U.S.C. Sec. 103 (a) over Stevenson *et al.* and Szalkowski *et al.*

Claims 10 and 12 have been rejected under 35 U.S.C. Sec. 103(a) as being unpatentable over Stevenson *et al.* (The Diabetes Manual, 1995 article) and Szalkowski *et al.* (Endocrinology, 1995 article).

As discussed above, neither asserted reference, alone or in combination teach or suggest therapeutic treatment of TNF-α mediated inflammatory disease. The asserted combination of art does not teach or suggest the claimed invention, or provide any reasonable expectation for success.

The Examiner's rejection is made using improper hindsight, using the teaching of the present application as a guide to interpreting the asserted art. This is not proper. There must be a suggestion to combine and modify the asserted combination of art other than the Examiner's improper use of hindsight.

Therefore, Applicants respectfully request withdrawal of the Sec. 103(a) rejection over Stevenson *et al.* and Szalkowski *et al.*

VI. Traverse of the Rejection under 35 U.S.C. Sec. 103 (a) over Ikeda *et al.* and Stevenson *et al.*

Claims 1-12 have been rejected under 35 U.S.C. Sec. 103(a) as being unpatentable over Ikeda *et al.* (U.S. Patent No. 6,133,293) and Stevenson *et al.* (The Diabetes Manual, 1995 article).

Ikeda et al. describe certain chemical compounds. As traversed above, Stevenson et al. do not fairly teach or suggest, with a reasonable expectation of success, the claimed method of the present invention. The Examiner's rejection is based upon the improper use of hindsight to reconstruct the claimed invention using the present application as a guide.

The Examiner's rejection is made using improper hindsight, with the benefit of the present application as a guide to interpreting the asserted art. The asserted combination of Ikeda et al. with Stevenson et al. do not teach or suggest the effective treatment of TNF-α mediated inflammatory disease by the method of the claimed invention. This rejection must be withdrawn.

Therefore, Applicants respectfully request withdrawal of the Sec. 103(a) rejection over Ikeda *et al.* and Stevenson *et al.*

VII. Traverse of the Double Patenting Rejection

Claims 1-12 have been rejected under the judicially-created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 5,965,584 in view of Stevenson *et al.* Claims 11 and 12 have been cancelled without prejudice.

Specifically, the Office Action stated that the one of ordinary skill in the art would have found it obvious to employ the present compounds in a method for treating or preventing inflammatory disease caused by TNF-alpha increase in a mammal.

As traversed above, the asserted combination of Ikeda et al and Stevenson *et al.* do not fairly teach or suggest, with a reasonable expectation of success, the claimed method of the present invention.

The Examiner's rejection is based upon the improper use of hindsight to reconstruct the claimed invention using the present application as a guide.

The asserted combination of art does not teach or suggest the claimed invention for treating inflammatory disease mediated by TNF-α. Neither Ikeda et al. nor Stevenson *et al.* teach or suggest the effective treatment of TNF-α mediated inflammatory disease by the method of the claimed invention.

Therefore, Applicants respectfully request withdrawal of the judicially-created obviousness-type double patenting rejection.

VIII. Conclusion

Reconsideration and allowance of the claims as amended is requested. Should the Examiner believe that a conference with Applicants' attorney would advance prosecution of this application, the Examiner is respectfully requested to call Applicants' attorney at the number below.

Respectfully submitted,

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